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Analysis of α -methylbenzyl thiourea inhibitors that target the putative VZV portal protein, pORF54

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Varicella-zoster virus (VZV) is the human herpesvirus that causes chickenpox and may reactivate within dorsal root ganglia leading to herpes zoster (shingles). Postherpetic neuralgia, a long-term, painfully debilitating disease, may result from reactivation. Currently, clinical treatment options for herpesvirus infections are limited to nucleoside analog drugs, like acyclovir, that act by interfering with viral DNA replication. These drugs are moderately effective at best and resistant viral strains may develop in immunocompromised hosts. Proteins involved in the VZV encapsidation process are promising novel targets for new drugs. Our laboratory is interested in the machinery involved in packaging genomic DNA into preformed viral capsids. Analogous to the DNA packaging process in bacteriophages, concatemeric viral DNA must be “guided” into the capsid through a series of steps. After the terminase-DNA complex interfaces with the portal protein, the viral genome is translocated inside the procapsid in an ATP-dependent manner, where the terminase-portal complex acts as a molecular motor. In 2003, Visalli *et al.* reported a novel class of α -methylbenzyl thiourea compounds that inhibited VZV replication by acting specifically on the portal protein. Understanding interactions between the portal protein and thiourea compounds could result in development of novel treatments that target the encapsidation process. VZV mutants resistant to one of the thiourea compounds were used to identify portal as the potential target (Visalli *et al.*, 2003). In the current study, IC_{50} data of additional compounds against both wild type and mutant strains suggest that compounds in the inhibitor series target the same protein, pORF54. Mutations identified from a panel of resistant isolates indicate a potential compound binding site that consists of multiple, non-linear regions of pORF54.
